Effect of home-based exercise intervention on fasting insulin and Adipocytokines in colorectal cancer survivors: a randomized controlled trial

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ARTICLE INFO

Article history:
Received 20 April 2017
Accepted 12 July 2017

Keywords:
Colorectal cancer survivors
Home-based exercise program
Insulin
Adipocytokines
Physical function

ABSTRACT

Background and Aims. Elevated circulating insulin is associated with increased risk of recurrence and cancer mortality in early-stage colorectal cancer (CRC). We conducted a randomized controlled trial to determine the effect of a 12-week home-based exercise program on fasting insulin, adipocytokines, and physical function in CRC survivors.

Methods. One hundred and twenty-three stage II-III CRC patients were randomly assigned to either a home-based exercise (n = 62) or standard care control group (n = 61) for 12 weeks. Home-based exercise consisted of aerobic and resistance training, with a goal of obtaining ≥18 metabolic equivalent task (MET)-h/wk. Participants in the exercise group were instructed to participate in >18 MET-h/wk. of aerobic and resistance exercise while the participants in the control group were asked to maintain their usual daily activity. The

Abbreviations: CRC, Colorectal cancer; MET, Metabolic equivalent task; TNF-α, Tumor necrosis factor-α; TC, Total cholesterol; TG, Triglycerides; HDL-C, High-density lipoprotein cholesterol; hs-CRP, High sensitivity C-reactive protein; LSI, Leisure score index.

Trial Registration number: ISRCTN47234641.

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http://dx.doi.org/10.1016/j.metabol.2017.07.005
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1. Introduction

Growing evidence suggests that more physically active colorectal cancer (CRC) survivors have lower risk of recurrence and colorectal cancer-specific mortality compared with those who are physically inactive [1–3]. Meyerhardt et al. [2] found that the adjusted hazard ratio for disease-free survival in stage III colon cancer patients was 0.51 (95% CI, 0.26 to 0.97) and 0.55 (95% CI, 0.33 to 0.91) for those who engaged in 18–26.9, and >27 metabolic equivalent task (MET)-hours per week of physical activity, respectively, compared to those that engaged in <3 MET-hours per week (e.g., 3 METs: any physical activity equivalent to walking at an average pace; 3 MET-hours per week: participating in 3 MET physical activity for an hour per week). A recent meta-analysis of seven prospective cohort studies found that CRC survivors who participated in any amount of physical activity, before and after the cancer diagnosis had 25% and 26% reduced risk of cancer-specific mortality, respectively [1]. However, the biological mechanisms underlying the impact of physical activity on the risk of recurrence and survival in CRC patients have not been fully elucidated.

The protective effect of physical activity on recurrence and cancer-related mortality could possibly be mediated through alterations of circulating insulin levels. Studies have shown that patients with type 2 diabetes have an increased risk of CRC [4], and that hyperinsulinemia could promote colorectal tumor growth and act as a cell mitogen [5,6]. Wolpin et al. [7] reported that among surgically resected CRC patients, high levels of prediagnosis plasma C-peptide, a more stable marker of insulin exposure, was associated with an increased risk of all-cause mortality. Therefore, lowering insulin levels may be one of the key strategies to improve prognosis of CRC patients.

In addition to insulin, recent studies also suggest that adipocytokines may affect the prognosis of CRC [8–10]. Tumor necrosis factor (TNF)-α is a cytokine produced by macrophages as well as tumor cells that may promote tumor growth during cancer progression. Serum TNF-α levels have been associated with clinical outcomes for several cancers, including colon cancer [11,12]. Adiponectin is a 30-kDa protein hormone and adipocytokine that shares homologies with TNF-α [13]. Previous studies have indicated that both of these adipocytokines may influence the growth and proliferation of tumor stroma and malignant cells. Low levels of adiponectin and high levels of TNF-α in circulation have been shown to be associated with risk and prognosis of diagnosis of CRC [11,14,15]. Regular exercise is known to lower insulin levels, increase circulating adiponectin levels and may also reduce TNF-α levels [16–19]. However, the effects of exercise on fasting insulin and circulating adipocytokines, such as TNF-α and adiponectin, have not been studied in CRC survivors.

Therefore, the purpose of this study was to examine the effect of a 12-week home-based exercise program on fasting insulin, adipocytokine and physical function in stage II–III CRC survivors following the completion of primary adjuvant therapy.

2. Methods

2.1. Setting and Participants

Participants were recruited from Yonsei Severance Hospital, Seoul, Republic of Korea between July 2011 and September 2013. Eligibility criteria were as follows: resident of Seoul or Gyeonggi-do; between 18 and 75 years of age; confirmed stage II to III CRC; completed surgery, radiotherapy, and/or chemotherapy within four weeks to two years prior to study enrollment; ECOG performance status of 0 or 1; ability to understand and provide written informed consent; and not planning extended absences in the three months subsequent to enrollment. Exclusion criteria were as follows: evidence of recurrent or metastatic disease; participation in regular structured physical activity at moderate-intensity exceeding 200 min/week; pregnant or planning to be pregnant within six months. We additionally excluded ostomy patients due to lack of evidence in safety of strength training.

For this two-arm 12-week randomized controlled trial, eligible patients with stage II–III CRC were randomly assigned to an exercise or standard care group before baseline measures by their primary physicians, in a 1:1 ratio using a computer-generated random number sequence. The allocation sequence was generated by a biostatistician using the Research Randomizer website program. All measurements were taken at baseline and after the 12-week intervention period at Yonsei Severance Hospital, by trained exercise specialists. The study was approved by the institutional review board of Yonsei Severance Hospital and all subjects provided written consent prior to the commencement of any study related procedures.
2.2 Exercise Intervention

The goal of the home-based exercise was to increase the participants’ level of physical activity to >18 MET-hours per week during the first six weeks [3]. After the 6th week, participants were encouraged to increase their level of physical activity to 27 MET-hours per week [2]. Participants were provided with an exercise diary and pedometer. All participants were encouraged to walk >10,000 steps per day. Of these 10,000 steps, participants were asked to complete 3000 steps as exercise that increased their heart rate up to 65% of their age-predicted maximum heart rate. Brisk walking, hiking and stationary bike riding were recommended for aerobic exercise. In addition, patients were provided with DVDs that contained two 30 min resistance exercise using their own body weight that could be performed daily at home. Following each exercise session, participants completed their exercise diary, and kept a record of daily steps, type of exercise and duration. The logs were checked by exercise specialists during weekly telephone counseling sessions and used to determine the appropriate intensity and duration of the exercise for the upcoming week. Exercise group participants visited the clinic three times during the 12-week intervention. The first appointment consisted of both a counseling session and an exercise session. During the one hour counseling session led by exercise specialist, participants learned about the benefits of exercise for CRC patients and during the exercise session, participants learned how to exercise correctly and followed the home-based exercise program. During the two additional appointments, exercise specialists confirmed that the participants were performing all exercises correctly. To increase the compliance of participants to exercise program, daily text message was sent to remind them. Patients in the standard care group were instructed to continue with their usual activities.

2.3 Measurements

Information regarding disease stage, adjuvant therapy, surgery and comorbidities were provided by participants and later confirmed by their physician and review of the medical records.

Participants were weighed on a digital scale, measurements were rounded up to the nearest 0.1 kg. Height was measured using a standard stadiometer (JENIX, Seoul, Korea), rounding up to the nearest 0.1 cm. Waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest with a plastic tape measure, rounding up to the nearest 0.1 cm. Assessment of body composition was performed using In-body IH-U070R (Biospace, Seoul, Korea).

Blood samples were collected after an overnight fast and stored in a –80 °C freezer until the time of assays. Levels of fasting glucose, total cholesterol (TC), triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were measured from serum using an ADVIA 1650 Chemistry system (Siemens, NY, USA). Fasting insulin was measured by chemiluminescence immunoassay (Roche, IN, USA). Insulin resistance was assessed using the HOMA-IR index fasting insulin (μIU/ml) × fasting glucose (mmol/L)/405. Levels of high sensitivity C-reactive protein (hs-CRP) was measured by a latex-enhanced immunoturbidimetric assay using an ADVIA 1650 Chemistry system (Bayer); the inter-assay and intra-assay reproducibilities were 2.70% and 2.55%, respectively. Adiponectin level was measured using an enzyme immunoassay kit (Mesdia, Seoul, Korea); inter-assay and intra-assay coefficients of variation were 4.5% and 4.6%. TNF-α level was measured using a commercially available enzyme-linked immunosorbent assay (R&D, Minneapolis, MN, USA); inter-assay and intra-assay coefficients of variation were 8.4% and 5.3%.

The six-minute walk test and the 30 s chair stand test from the Senior’s Fitness Test was adopted to test the participant’s physical function and lower body strength, respectively. All measurements were conducted in accordance with the manual [20].

Upper body strength and endurance were measured using the push up test, and handgrip strength was measured using a handgrip dynamometer to assess the maximal voluntary grip strength [21]. Men performed the standard ‘push up’ and women performed the ‘knee push up’; beginning with the hands and knees touching the floor, the body and legs in a straight line, the feet were raised in the air, keeping the back and knees straight, the subject lowers the body until there is a 90-degrees angle at the elbows, then returns back to the starting position with the arms extended. The level of weekly exercise participation was assessed using the leisure score index (LSI) of the Godin Leisure-Time Exercise Questionnaire [22,23]. It has been routinely used in many intervention studies [24] and its validity has been tested [25]. We modified the LSI to include average duration of exercise in minutes. The LSI was calculated by multiplying the average frequency by the average duration for each intensity level. Low intensity exercises (e.g., walking) were converted to 3 METs, moderate exercises (e.g., brisk walking and resistance exercise) to 4 METs, and vigorous exercises (e.g., running, hiking, and vigorous resistance exercise) to 6 METs.

2.4 Sample Size

A previous study in breast cancer patients [26] indicated that enrolling 50 patients per group would give 80% power with a two-sided α = 0.05 to detect a mean difference in the change of insulin levels of 2.6 μU/ml between the exercise and control groups, assuming equal variance and a standard deviation of 4.0 μU/ml. We enrolled 60 patients per group to account for an anticipated dropout rate of approximately 20%.

2.5 Statistical Analysis

All primary analyses were conducted using an intention to treat analysis, with the last observation carry-forward principle being used for missing data. Data were analyzed using SPSS (v.22; IBM Software, Armonk, NY, USA). Baseline characteristics of the intervention and standard care group were compared using the independent-samples student t-test or Mann-Whitney U test for continuous data and the chi-square test for categorical data. Two-way repeated measures ANCOVA analysis of variance was calculated with the intervention period as the within-subject factor and with the intervention as the between-subject factor, adjusting for cancer stage. Moreover, subgroup analyses were performed
stratified by gender, location of cancer (colon vs. rectum),
cancer stage (stage II vs. III) and fasting glucose impairment
(<100 mg/dl vs. ≥100 mg/dl). For each subgroup, standard
mean differences from control group were calculated. All
analyses were tested with a significance level of \( p < 0.05 \).

3. Results

During the study period, 2914 patients were screened for
eligibility and 725 patients met the inclusion criteria. One
hundred twenty-three participants agreed to participate in
the study and were randomly assigned at a ratio of 1:1 to
exercise (\( n = 62 \)) or standard care (\( n = 61 \)). After 12 weeks, the
retention rate was 82.3% for the exercise group and 78.7% for
standard care group. Among participants who dropped out of
the study, one third of them dropped out of the study due to
cancer recurrence or medical conditions, not related to the
current study. There are two participants in the exercise
group experienced cancer recurrence (\( n = 1 \)) or metastasis
(\( n = 1 \)) and both cases were found during the first six weeks of
the study and were not related with exercise intervention
implemented in our study. Fig. 1 shows participant flow and
loss to follow-up.

3.1. Baseline Characteristics

Baseline characteristics were similar between groups (Table 1).
Mean age was 56.3 ± 9.7 years and the average BMI was 23.5 ±
3.3 kg/m². Among participants, 68.9% had colon cancer, and the
average time since completion of therapy was 9.8 ± 6.3 months.

3.2. Self-reported Physical Activity Change

In the exercise group, self-reported vigorous physical activity
was increased from 6.2 ± 33.1 min per week to 43.9 ± 102.4 min
per week, and self-reported moderate physical activity
from 126.7 ± 215.8 min per week to 332.8 ± 307.9 min per
week (Table 2). In MET hours per week, moderate-vigorous
physical activity participation increased from 9.1 ± 14.7
MET hours per week to 26.6 ± 21.7 MET hours per week in the exercise group, with no change in control (group and time interaction, \( p < 0.01 \)). At week 12, 44 out of 51 participants (86.3%) exceeded the target of physical activity level of >18 MET hours per week and 38 participants (74.5%) exceeded a total physical activity level of 27 MET hours per week.

### 3.3. Primary Outcome

In response to the exercise intervention, circulating insulin level decreased by 1 \( \mu \text{U/ml} \) (6.0 ± 3.9 vs. 5.0 ± 3.5, \( p = 0.009 \)) in the exercise group with no change in the control group (\( p = 0.022 \)). We have also analyzed our data after excluding those who did not complete the study (per-protocol) and found similar result as the intention-to-treat analysis.

### 3.4. Secondary Outcomes

Table 3 shows the changes in body composition and biomarkers over the 12-week intervention in the exercise and control group. The level of adiponectin significantly increased over the 12 weeks in both exercise and control groups, and there was no significant difference between groups. TNF-\( \alpha \) levels decreased non-statistically significant level (Pre: 1.93 ± 2.06 vs. Post: 1.78 ± 2.38, \( p = 0.388 \)) in the exercise group while it significantly increased in the control group.

### Table 1 – Baseline demographic and medical profiles of participants overall and by group assignment.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (( n = 123 ))</th>
<th>Exercise (( n = 62 ))</th>
<th>Standard care (( n = 61 ))</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>56.3 ± 9.7</td>
<td>56.3 ± 9.7</td>
<td>56.3 ± 9.9</td>
<td>0.985</td>
</tr>
<tr>
<td>Sex, male</td>
<td>59 (48.0)</td>
<td>31 (50)</td>
<td>28 (45.9)</td>
<td>0.719</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td></td>
<td>0.506</td>
</tr>
<tr>
<td>Married</td>
<td>100 (81.3)</td>
<td>51 (82.3)</td>
<td>49 (80.3)</td>
<td></td>
</tr>
<tr>
<td>Widowed</td>
<td>8 (6.5)</td>
<td>5 (8.1)</td>
<td>3 (4.9)</td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>5 (4.1)</td>
<td>1 (1.6)</td>
<td>4 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>10 (8.1)</td>
<td>5 (8.1)</td>
<td>5 (8.2)</td>
<td></td>
</tr>
<tr>
<td>Completed university</td>
<td>60 (48.8)</td>
<td>36 (58.1)</td>
<td>24 (39.3)</td>
<td>0.151</td>
</tr>
<tr>
<td>Income &gt;$3000/month</td>
<td>55 (44.7)</td>
<td>31 (50.0)</td>
<td>24 (39.3)</td>
<td>0.278</td>
</tr>
<tr>
<td>Vigorous physical activity, (min/wk)</td>
<td>9.3 ± 57.4</td>
<td>6.2 ± 33.1</td>
<td>12.4 ± 74.3</td>
<td>0.986*</td>
</tr>
<tr>
<td>Moderate physical activity, (min/wk)</td>
<td>118.5 ± 206.1</td>
<td>126.7 ± 215.8</td>
<td>110.1 ± 197.4</td>
<td>0.428*</td>
</tr>
<tr>
<td>Current smoker</td>
<td>24 (19.5)</td>
<td>16 (25.8)</td>
<td>8 (13.1)</td>
<td>0.204</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>9 (7.3)</td>
<td>2 (3.2)</td>
<td>7 (11.5)</td>
<td>0.095</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>62.9 ± 10.7</td>
<td>63.0 ± 9.4</td>
<td>62.9 ± 12.0</td>
<td>0.951</td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>23.5 ± 3.3</td>
<td>23.5 ± 3.0</td>
<td>23.5 ± 3.6</td>
<td>0.878</td>
</tr>
<tr>
<td>Cancer type</td>
<td></td>
<td></td>
<td></td>
<td>0.558</td>
</tr>
<tr>
<td>Colon</td>
<td>84 (68.9)</td>
<td>44 (72.1)</td>
<td>40 (65.6)</td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>38 (31.1)</td>
<td>17 (27.9)</td>
<td>21 (34.4)</td>
<td></td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
<td></td>
<td></td>
<td>0.046</td>
</tr>
<tr>
<td>II</td>
<td>57 (46.7)</td>
<td>34 (55.7)</td>
<td>23 (37.7)</td>
<td></td>
</tr>
<tr>
<td>Ill</td>
<td>65 (53.3)</td>
<td>27 (44.3)</td>
<td>38 (62.3)</td>
<td>0.773</td>
</tr>
<tr>
<td>Cancer treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>98 (80.3)</td>
<td>48 (78.7)</td>
<td>50 (82.0)</td>
<td></td>
</tr>
<tr>
<td>Chemotherapy + radiotherapy</td>
<td>13 (10.7)</td>
<td>6 (9.8)</td>
<td>7 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Time since completion of therapy, months</td>
<td>9.8 ± 6.3</td>
<td>10.7 ± 8.8</td>
<td>8.8 ± 7.2</td>
<td>0.102</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or \( n \) (%). *Mann-Whitney U test was employed since data was not normally distributed. Abbreviation: BMI: body mass index.

### Table 2 – Change in physical activity levels and fitness parameters over the 12-week exercise intervention.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise group (( n = 62 ))</th>
<th>Standard care group (( n = 61 ))</th>
<th>Repeated measures ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 12-week</td>
<td>Baseline 12-week</td>
<td>Group Time Group × time</td>
</tr>
<tr>
<td>Chair stand</td>
<td>19.4 ± 6.6</td>
<td>22.1 ± 5.8*</td>
<td>22.8 ± 6.5</td>
</tr>
<tr>
<td>Push up</td>
<td>14.8 ± 9.6</td>
<td>19.5 ± 11.8*</td>
<td>14.3 ± 12.2</td>
</tr>
<tr>
<td>Handgrip(L)(kg)</td>
<td>30.7 ± 9.7</td>
<td>31.5 ± 9.9*</td>
<td>29.4 ± 8.7</td>
</tr>
<tr>
<td>Handgrip(R)(kg)</td>
<td>32.4 ± 10.3</td>
<td>32.9 ± 10.4</td>
<td>31.5 ± 9.5</td>
</tr>
<tr>
<td>6 min walk (m)</td>
<td>578.1 ± 79.4</td>
<td>603.3 ± 74.9*</td>
<td>598.1 ± 75.2</td>
</tr>
<tr>
<td>VPA (min/wk)</td>
<td>6.2 ± 33.1</td>
<td>43.9 ± 102.4*</td>
<td>12.4 ± 74.4</td>
</tr>
<tr>
<td>MPA (min/wk)</td>
<td>126.7 ± 215.8</td>
<td>332.8 ± 307.9*</td>
<td>110.1 ± 197.4</td>
</tr>
</tbody>
</table>

2-way repeated measures ANCOVA was performed to determine independent effect of group, intervention(time), and interaction after adjustment for cancer stage; data presented as mean ± SD \( p < 0.05 \) difference between baseline and at 12-week. Abbreviation: SD, standard deviation; VPA, vigorous physical activity; MPA, moderate physical activity.
Therefore, there was significant group and time interaction for TNF-α (p = 0.030). There was no significant group and time interaction for body weight, waist circumference, glucose, TG, TC, HDL-C, hs-CRP or adiponectin.

Table 2 shows the changes in physical function over the 12-week intervention period. Participants in the exercise group demonstrated significantly greater improvement in push-up (p < 0.001), chair stand (p = 0.005), and handgrip strength (p = 0.047) compared to participants in the control group. Six-minute walk distance increased by 25.2 m in the exercise group with no change in the control group (p = 0.061 for group and time interaction).

3.5. Subgroup Analyses

Since gender, cancer stage, location of cancer and fasting glucose levels could potentially modify the findings, further subgroup analyses were performed (Fig. 2). There were no significant interactions between by gender, location of cancer, and cancer stage. However, subgroup analysis of fasting glucose levels showed a significant reduction (p = 0.018) in circulating insulin levels only in those with impaired fasting glucose or type 2 diabetes (fasting glucose ≥ 100 mg/dl) while no significant difference was observed in participants with normal glucose levels.

4. Discussion

In our study, we have examined whether a 12 week of home-based exercise participation would reduce circulating insulin and adipocytokine levels in stage II-III colorectal cancer patients completed cancer treatment. As hypothesized, our home-based exercise intervention resulted in significant reduction in circulating insulin levels in conjunction with

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### Table 3 – Change in body composition and biomarkers over the 12-week exercise intervention.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exercise group (n = 62)</th>
<th>Standard care group (n = 61)</th>
<th>Repeated measures ANCOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12-week</td>
<td>Baseline</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>63.0 ± 9.4</td>
<td>63.0 ± 9.4</td>
<td>62.9 ± 12.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 ± 3.0</td>
<td>23.6 ± 2.8</td>
<td>23.5 ± 3.6</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>27.2 ± 8.3</td>
<td>26.6 ± 8.1</td>
<td>28.0 ± 8.0</td>
</tr>
<tr>
<td>Lean mass (kg)</td>
<td>25.4 ± 5.3</td>
<td>25.4 ± 5.2</td>
<td>24.6 ± 5.4</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>82.5 ± 8.8</td>
<td>82.0 ± 8.6</td>
<td>82.2 ± 9.6</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>94.1 ± 13.9</td>
<td>94.5 ± 14.9</td>
<td>96.0 ± 18.1</td>
</tr>
<tr>
<td>Insulin (μU/ml)</td>
<td>6.0 ± 3.9</td>
<td>5.0 ± 3.5*</td>
<td>7.1 ± 4.1</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.35 ± 0.94</td>
<td>1.16 ± 0.85*</td>
<td>1.78 ± 1.13</td>
</tr>
<tr>
<td>TG (mg/dl)</td>
<td>112.9 ± 71.1</td>
<td>115.7 ± 76.7</td>
<td>123.0 ± 53.8</td>
</tr>
<tr>
<td>TC (mg/dl)</td>
<td>191.1 ± 35.4</td>
<td>185.5 ± 34.6*</td>
<td>193.1 ± 38.6</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>56.0 ± 14.6</td>
<td>54.5 ± 14.9</td>
<td>52.9 ± 12.8</td>
</tr>
<tr>
<td>hs-CRP (mg/dl)</td>
<td>0.74 ± 0.92</td>
<td>0.72 ± 0.93</td>
<td>0.95 ± 1.32</td>
</tr>
<tr>
<td>Adiponectin (μg/ml)</td>
<td>11.7 ± 7.2</td>
<td>13.2 ± 7.3*</td>
<td>13.2 ± 6.6</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>1.93 ± 2.06</td>
<td>1.78 ± 2.38</td>
<td>1.39 ± 0.76</td>
</tr>
</tbody>
</table>

2-way repeated measures ANOVA was performed to determine independent effect of group, intervention(time), and interaction after adjustment for cancer stage; data presented as mean ± SD *p < 0.05 difference between baseline and at 12-week. Abbreviation: SD, standard deviation; BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglycerides; TC, total cholesterol; hs-CRP, high sensitivity C-reactive protein; TNF-α, tumor neurosis factor-α.

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![Fig. 2 – Subgroup analysis of adjusted group difference of mean change in insulin levels.](image-url)
improved physical function. We also observed significant difference in TNF-α levels in response to exercise intervention between groups, however, although significant difference between groups could be more due to increase in TNF-α level observed in the standard care group.

Fasting serum insulin and C-peptide levels are positively associated with increased risk of CRC and mortality [5–7, 27]. In our study, we have observed significant reduction in insulin levels in response to the home-based exercise intervention. Given that insulin is a strong mediator of colorectal carcinogenesis, our findings from the current study that exercise positively altered the serum insulin levels in CRC survivors may address the importance of exercise in a clinical setting. Interestingly, our subgroup analysis further showed that insulin reduction was more evident among participants whose fasting glucose level was higher than 100 mg/dl. Knowing that colorectal cancer survivors with impaired glucose and type 2 diabetes have increased risk of mortality [28, 29], the importance of exercise for these subgroup of colorectal cancer survivors was confirmed in our study. However, it is difficult to draw conclusion to link between reduction in circulating insulin level and better prognosis based on the finding from the current study. Furthermore, it is difficult to address how the amount of insulin reduction observed in our study is clinically relevant since there is no cut point to identify circulating insulin level, which may associate with increased colorectal cancer risk. Therefore, it is important to perform a randomized controlled trial with recurrence free survival as primary outcome and other biomarkers to clearly identify the role of exercise intervention on prognosis of colorectal [30].

We hypothesized that the exercise intervention would not only decrease circulating insulin, but also decrease hs-CRP, TNF-α and increase adiponectin levels. However, the biomarkers did not show the trends that were expected. We observed significant increases in adiponectin level for both groups. There was also no significant change in hs-CRP after the intervention in either group. Previous studies that have examined the effect of exercise on circulating adipocytokines and hs-CRP levels among breast cancer survivors also found inconsistent results with interventions which included aerobic and/or resistance exercise, and lifestyle changes that combined exercise with diet that ranged from 12 weeks to 1 year in duration [26, 31–38]. For TNF-α, there was a significant difference in the adjusted difference in mean change between the exercise group and the standard care group, but this significance is more attributable to the increase in TNF-α in the standard care group as opposed to the expected decrease in TNF-α of the exercise group. Reasons for such unexpected trends in biomarkers are uncertain and thus more research need to be done before any conclusions are made.

Previous studies reported that physical activity may reduce cancer recurrence and mortality in CRC survivors [39, 40]. Considering the amount of physical activity associated with improved cancer prognosis from Meyerhardt’s study (18MET-hours per week) [2], we encouraged participants to achieve 18 to 27 MET-hours per week of moderate to vigorous physical activity, and the exercise group participated in 376.7 ± 311.7 min per week, which is equivalent to 30.0 ± 21.9 MET-hours per week. During the 12-week intervention, most participants met the physical activity guidelines for cancer survivors, and almost tripled the amount of physical activity that they participated in at the baseline. They also experienced improvements in most measurements of physical function.

The present study had several limitations. First, physical activity was measured using a self-reported questionnaire, which may underestimate or overestimate the physical activity level. Second, the duration of the exercise intervention was relatively short, and we do not know whether the observed changes can be maintained or the long-term implications of such changes. Third, we have not analyzed participants diet before and after the intervention and therefore we cannot exclude the possibility that the significant reduction in percent body fat and circulating insulin level in exercise group could be due to change in diet between groups. Finally, the current study is single-center study and, this one should be careful in generalizing the findings of the study.

In conclusion, a 12-week home-based exercise program significantly reduced fasting insulin and improved physical function in stage II-III CRC survivors. Further studies are needed to investigate the physiologic changes that exercise induces in CRC survivors and whether changes in biomarkers such as insulin are associated with improvements in CRC prognosis.

Author Contributions

JJ, NKK, SHC, and JWL designed the trial, led the conduction of the trial. MKL, JYK, DIK, DWK, JHP, KYA, HYI, and DHL contributed to the data collection. MKL, YHR, and JJ analyzed the data. MKL and JJ let the conduction of the trial, data interpretation and participated in writing manuscript. JM and JJ discussed the data and made revision. All authors and edited the manuscript and approved the final version.

Acknowledgment

This research was supported by the National R&D program for Cancer Control, Ministry of Health and Welfare, Republic of Korea (1631020) and the National Research Foundation of Korea (NRF-2015S1A5B8036349).

Conflicts of Interest

The authors declare no conflicts of interest.

Appendix A.
Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.metabol.2017.07.005.
REFERENCES


